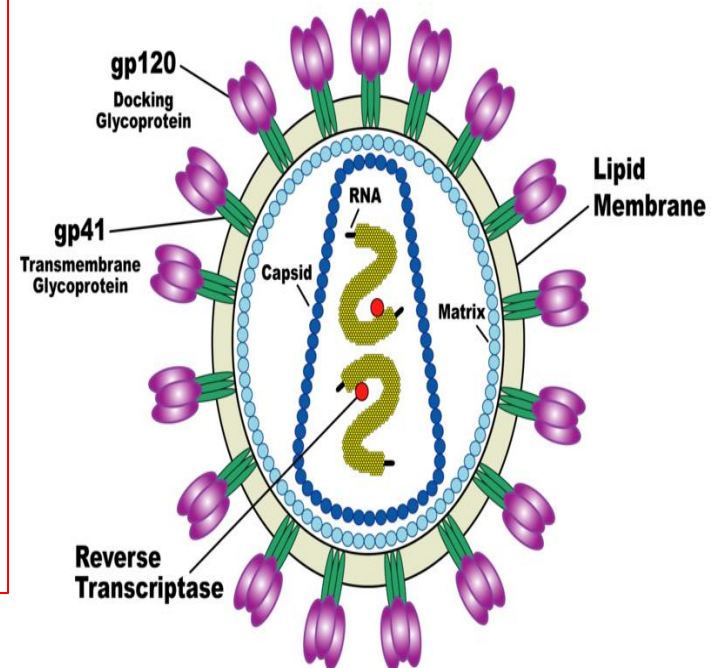
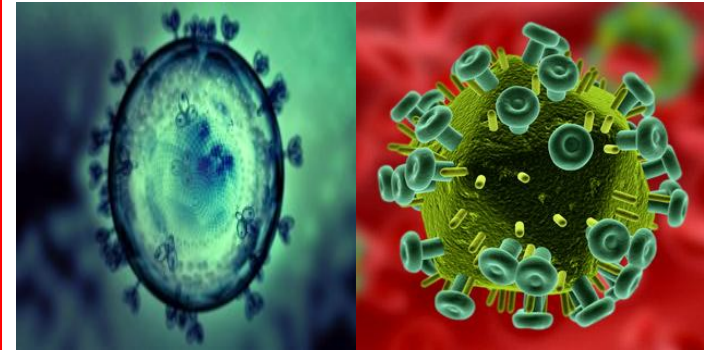


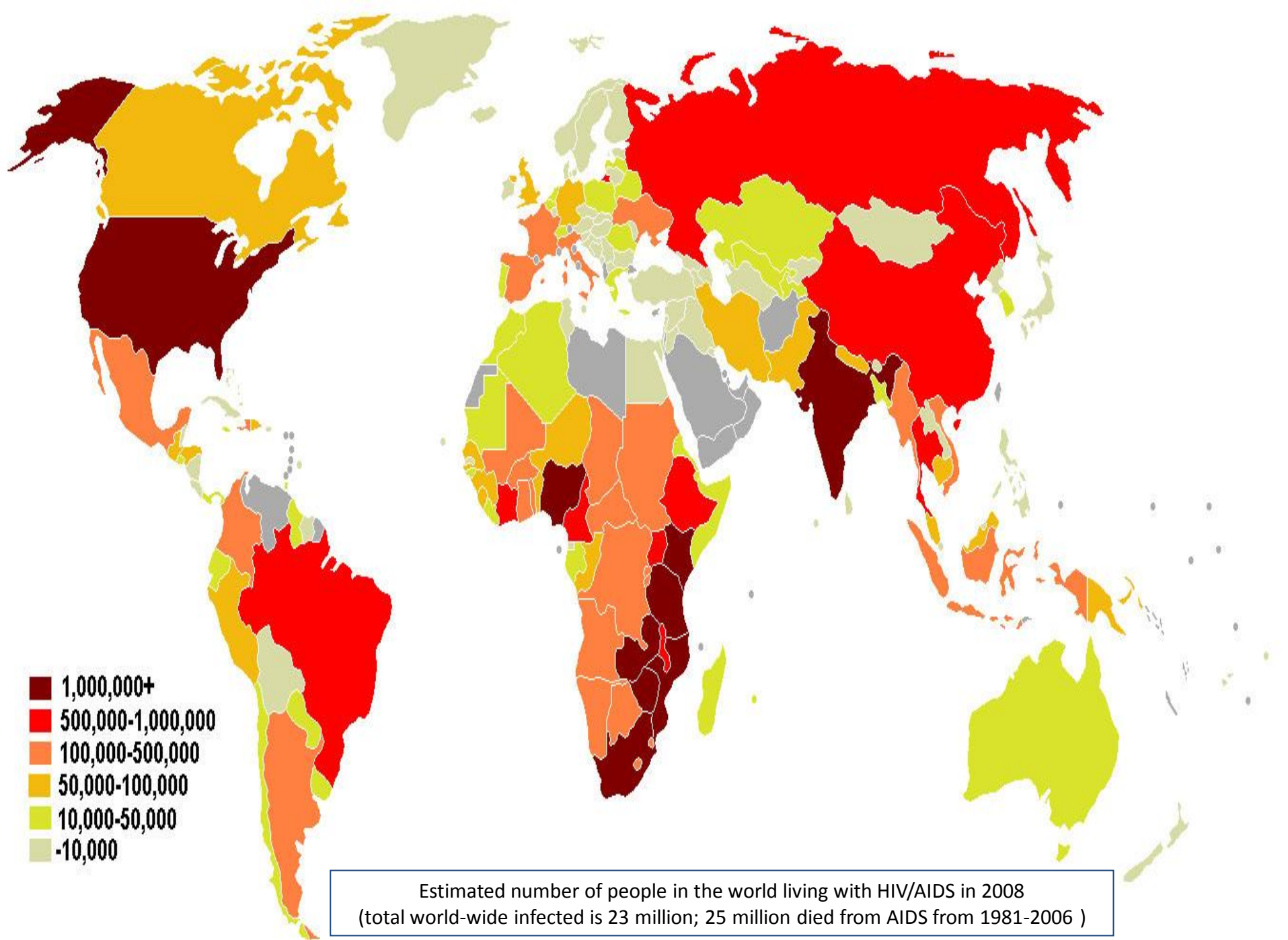
Drug used in AIDS

Lecture-5-
Reproductive Block
Ahlam Sultan

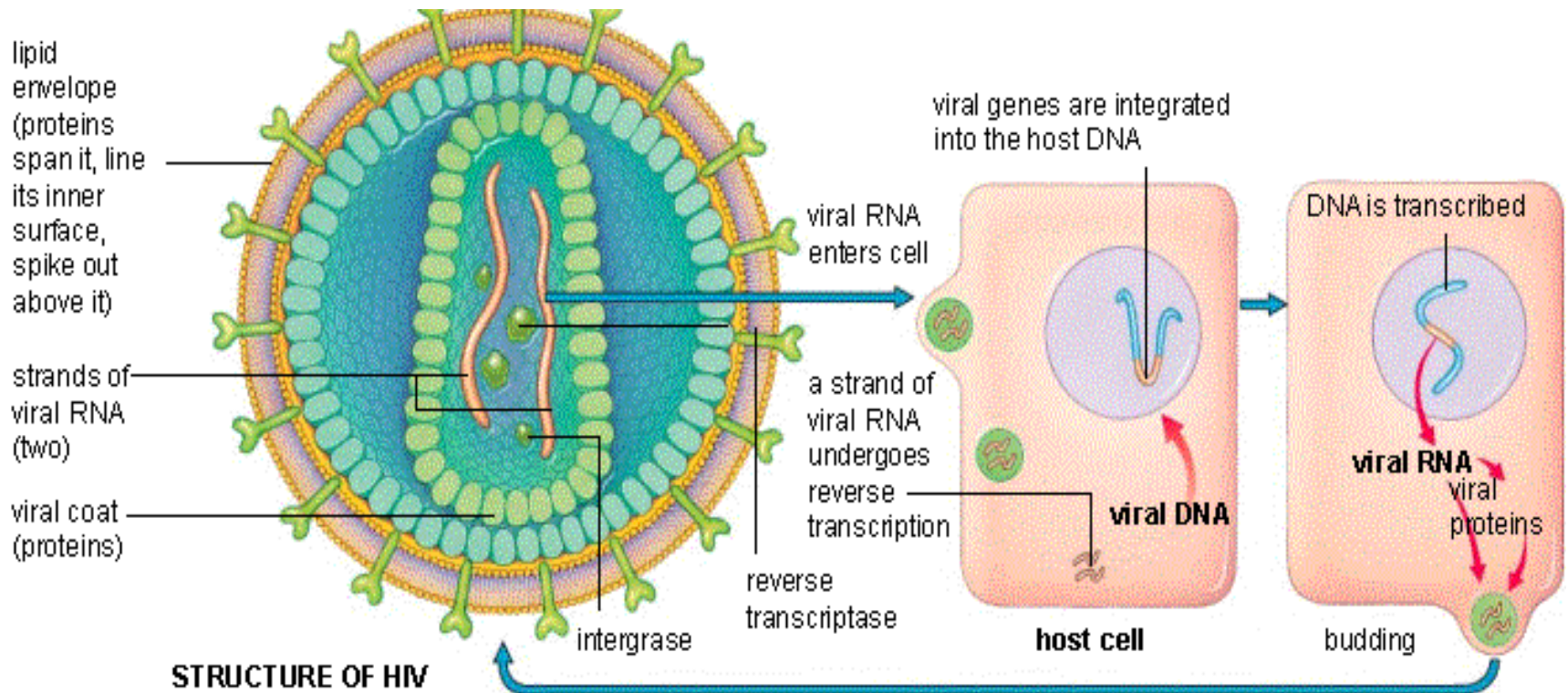
HIV infection

- There is no cure for infection caused by the human immunodeficiency virus (HIV) but a number of drugs **slow disease progression**
- Drugs for HIV infections (**antiretrovirals**) may be associated with serious side-effects
- **Treatment should be started before the immune system is irreversibly damaged**
- Commitment to treatment and strict adherence over many years required



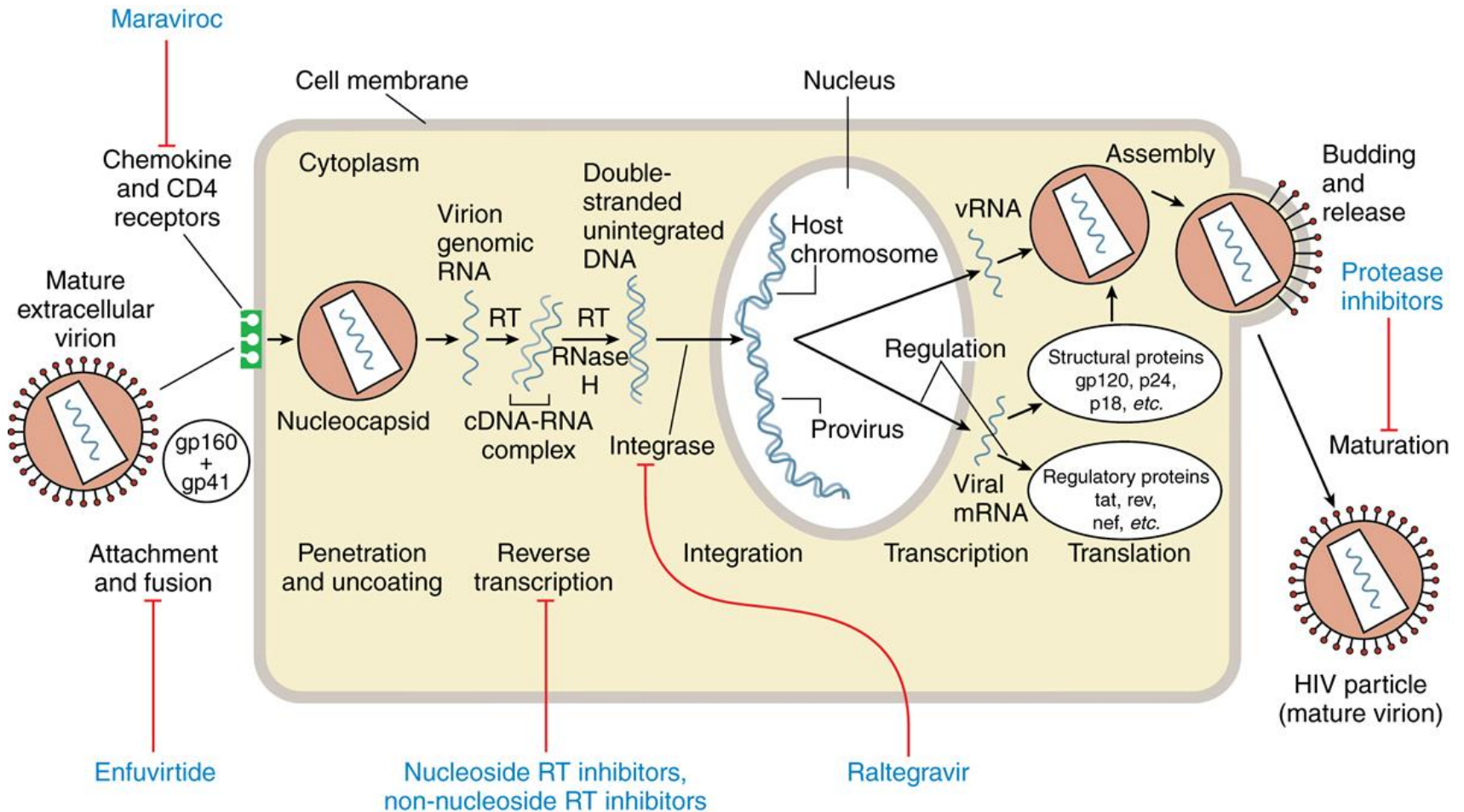


HIV Replication



- **RNA retroviruses (HIV)** contain an enzyme, **reverse transcriptase**, which makes a DNA copy of the viral RNA. This **DNA copy is integrated** into the host cell genome and direct the generation of new virus

Major sites of Antiretroviral Drugs



Replicative cycle of HIV-1 showing the sites of action of available antiretroviral agents

Classes of Antiretroviral agents

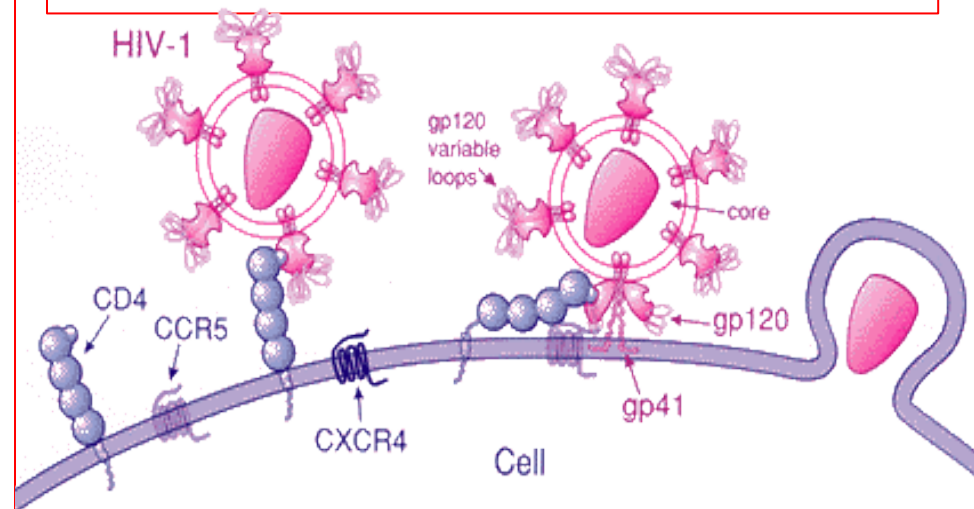
- 1. Reverse transcriptase inhibitors (RTIs), prevent replication**
 - a- Nucleoside RTIs (NRTIs)
 - b- Non- Nucleoside RTIs (NNRTIs)
- 2. Protease inhibitors** that prevent viral protein processing
- 3. Inhibitors of HIV integrase** that prevent the incorporation of viral DNA into the host genome
- 4. Inhibitors of HIV fusion**
- 5. Inhibitors of viral entry** block the use of host cell surface receptors that are used as entry points by viruses

HIV infection



- There are two major families of HIV:
 - ✓ HIV-1
 - ✓ HIV-2
- They have **similar** in-vitro sensitivity to most antiretroviral drugs
- **NNRTs** are HIV-1 specific and have no activity against HIV-2

- HIV targets are the CD4 receptor and coreceptor, **chemokine receptor** (**CCR5** or **CXCR4**), present on **T-Lymphocyte**



HIV treatment

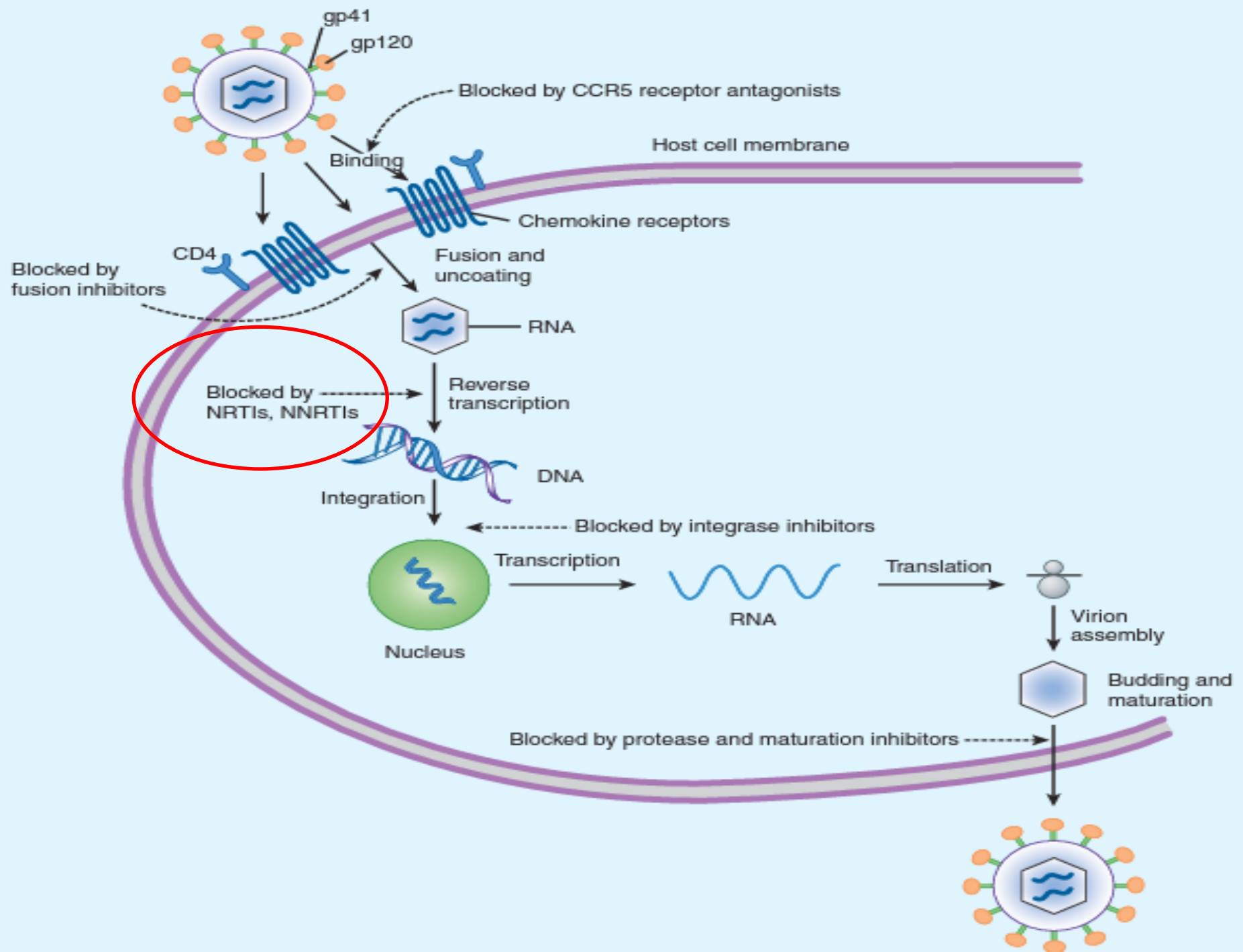


- HIV has high mutation rate and therefore easily developed resistance to the drugs, multidrug resistance strains have emerged and thus makes the treatment more difficult
- The development of resistance is reduced by using **combination** of drugs
- Using Highly active antiretroviral therapy (HAART) regimen suppresses HIV replication and prolong patients survival
- The current recommendation for primary therapy is to administer two NRTIs with either a protease inhibitor or an NNRTIs

1. Reverse Transcriptase Inhibitors (RTIs)

I. Nucleoside RTIs (NRTIs)	Common Therapeutic Indication
Zidovudine, abacavir, lamivudine, didanosine, emtricitabine, stavudine, tenofovir	-Mainly HIV, generally in combination - Lamivudine also used in Hepatitis B
II. Non-Nucleoside RTIs (NNRTIs)	Common Therapeutic Indication
Efavirenz, Nevirapine, Etravirine, Rilpivirine	-Used commonly in the treatment of HIV





I. Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

E.g.,

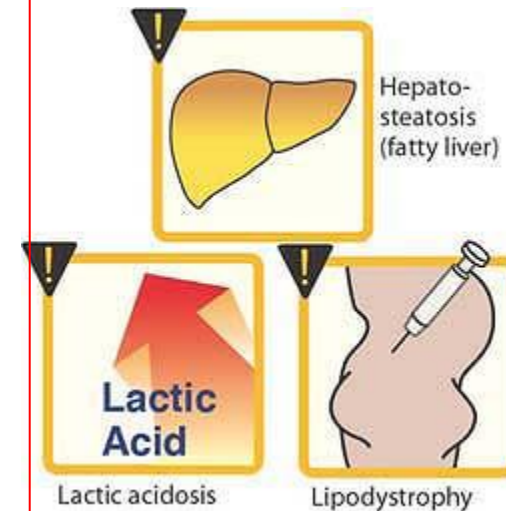
Zidovudine
Abacavir
Lamivudine
Didanosine
Emtricitabine
Stavudine
Tenofovir

MOA:

- NRTIs **inhibit reverse transcriptase enzyme**, which convert viral RNA into proviral DNA that is then incorporated into a host cell chromosome
- NRTIs are phosphorylated by host cell enzymes to give the 5'-triphosphate, which competes with equivalent host cellular **triphosphates** that are essential substrates for the reverse transcriptase enzyme

NRTIs

- The selective toxicity of these drugs depends on their ability to inhibit the HIV reverse transcriptase without inhibiting host cell **DNA polymerases**, which is mitochondrial enzyme
- As a result, the important toxicities common to this class of drugs are part of inhibiting DNA polymerase
- **SE:**
 1. Peripheral neuropathy
 2. Myopathy
 3. fatal liver toxicity characterized by **lactic acidosis** and hepatomegaly with steatosis
 4. BM suppression(e.g., anemia, neutropenia)
 5. Pancreatitis
 6. **Lipodystrophy syndrome**



Some adverse reactions
of nucleoside analogs

Lipodystrophy Syndrome

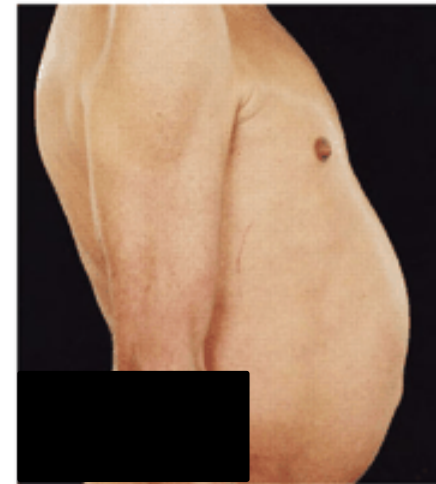
- Is a metabolic effect associated with **antiretroviral treatment** include:
 - ✓ Fat redistribution
 - ✓ Insulin resistance
 - ✓ Dyslipidaemia
- It is a risk factor for **CVD**
- Plasma lipids and blood glucose should be monitor



fat wasting



buffalo hump



Central obesity

Zidovudine (AZT)

Uses:

- 1- Approved for the treatment of adults and children with HIV infection (**drug of choice**)
- 2- For **HIV positive pregnant lady**, AZT is given during pregnancy and continue in new born for 6 weeks, AZT reduce risk of transmission to the baby
- 3- Post-exposure prophylaxis in HIV-exposed healthcare worker

- Combination therapy of AZT with other antiretroviral drugs gives better results
- Marketed in oral tablets, capsules and solution as well as IV
- Is available in coformulated tablets with lamivudine or with lamivudine and abacavir

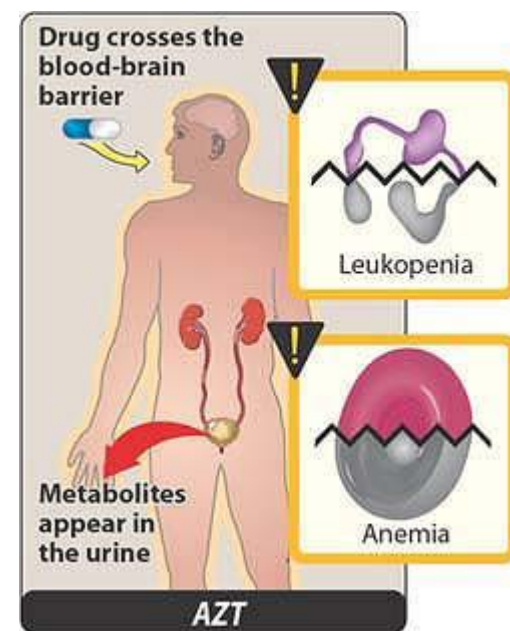


Zidovudine (AZT)

- The drug is well absorbed after oral administration

SE:

1. BM suppression (anemia, granulocytopenia)
2. Headache (common)
3. Nail hyperpigmentation



Administration,
metabolism, and
toxicity of
zidovudine (AZT)

Abacavir, Lamivudine Didanosine, Emtricitabine, Stavudine, Tenofovir

- Are other NRTIs effective against AZT resistant HIV infections
- They are used as alternatives to AZT or with AZT in patient with advanced HIV who are intolerant to AZT or not responding to AZT



II. Non-Nucleoside Reverse transcriptase inhibitors (NNRTIs)

E.g,

Efavirenz
Nevirapine

- Used commonly in the treatment of HIV-1 but not HIV-2 infection

- Most of NNRTIs are **inducers**, **substrates** or **inhibitors** to varying degree of liver cytochrome P450 enzymes



NNRTIs

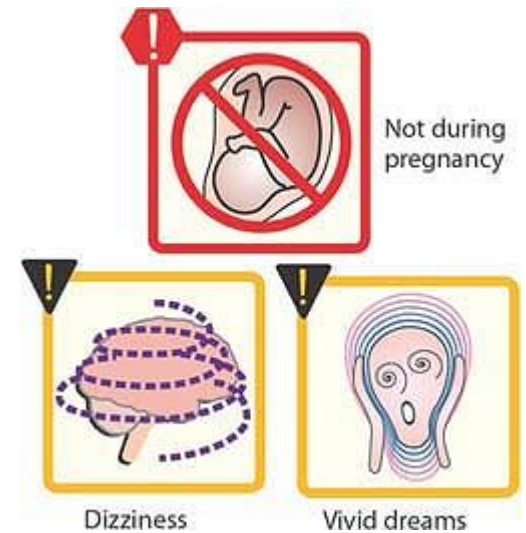
- **MOA:**
 - ✓ They are chemically diverse compounds that bind to HIV-1 reverse transcriptase and inactivate it
- These drugs doesn't required phosphorylation for activation
- Have no activity against host cell DNA polymerase
- NNRTIs are susceptible to high level of drug resistance, for this reason they must be combined with at last 2 other drugs

- **Nevirapine** is used in pregnant women during labor and in newborn to **prevent mother-to-newborn transmission of HIV**

NNRTIs

Adverse Effects:

1. Rash (common)
2. CNS effect (e.g., insomnia, bad dreams & psychotic symptoms) esp. with efavirenz
3. Efavirenz is teratogenic



Adverse reactions of *efavirenz*

2. Protease Inhibitors

E.g,

Saquinavir
Nelfinavir
Indinavir
Ritonavir
Amprenavir
Lopinavir

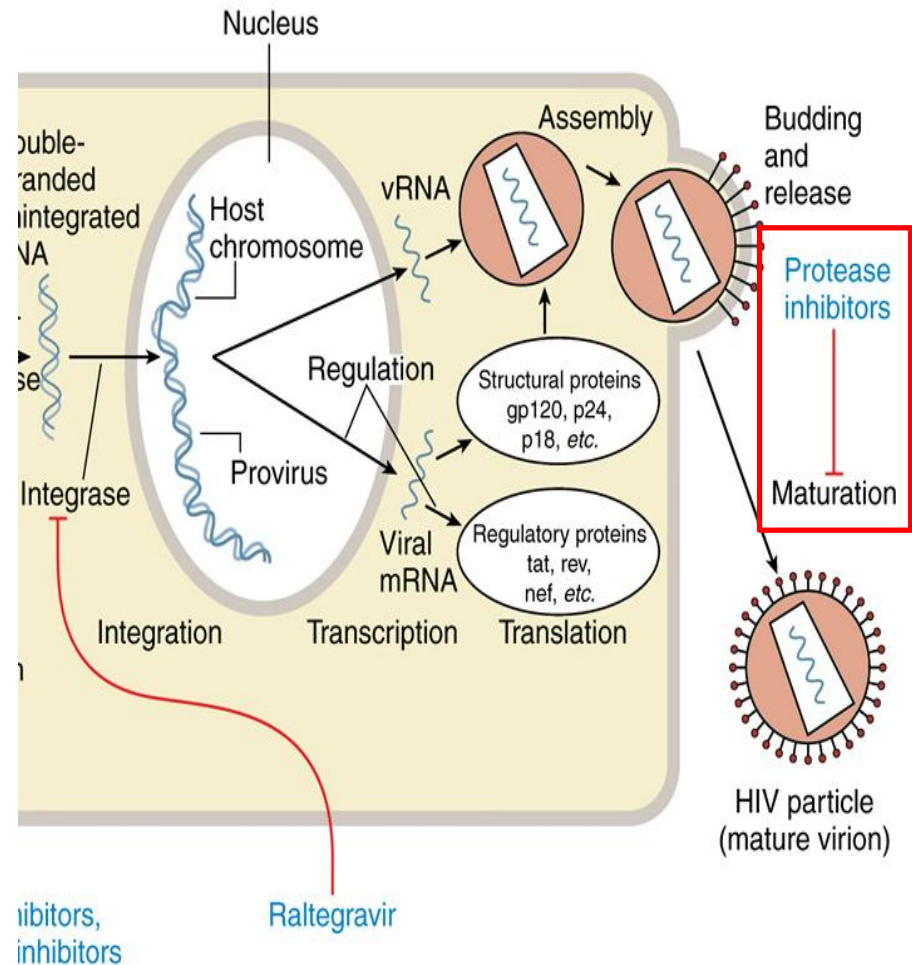
- Used in the treatment of HIV
- They are **used in combination with RTIs**
- *All inhibit liver CYP450 enzyme*



Protease Inhibitors

MOA:

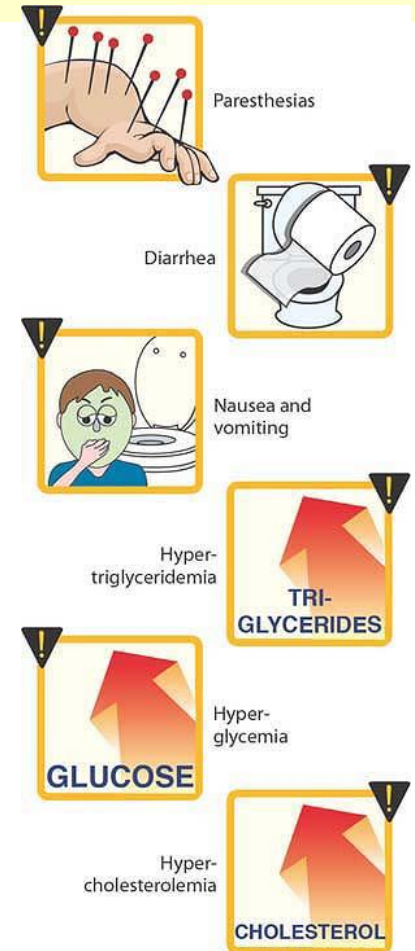
- They prevent viral maturation by binding to HIV protease



Protease Inhibitors

SE:

1. Diarrhea, N&V (common)
2. Paresthesias
3. Hyperglycemia
4. Hypertriglyceridemia, hypercholesterolemia
5. **Lipodystrophy syndrome**
6. Drug-drug interaction



Some adverse effects of the HIV protease inhibitors

Contraindication:

DRUG CLASS	EXAMPLE
ANTIARRHYTHMICS	<i>Quinidine</i>
ERGOT DERIVATIVES	<i>Ergotamine</i>
ANTIMYCOBACTERIAL DRUGS	<i>Rifampin</i>
BENZODIAZEPINES	<i>Triazolam</i>
INHALED STEROIDS	<i>Fluticasone</i>
HERBAL SUPPLEMENTS	St. John's wart
HMG CoA REDUCTASE INHIBITORS	<i>Lovastatin</i> <i>Simvastatin</i>
NARCOTICS	<i>Fentanyl</i>



Contraindicated

PROTEASE INHIBITORS

Caution:

DRUG CLASS	EXAMPLE
ANTICOAGULANTS	<i>Warfarin</i>
ANTICONVULSANTS	<i>Phenytoin</i>
ANTIFUNGALS	<i>Voriconazole</i>
ANTIMYCOBACTERIALS	<i>Ribabutin</i>
ERECTILE DYSFUNCTION AGENTS	<i>Sildenafil</i> <i>Tadalafil</i> <i>Vardenafil</i>
LIPID-LOWERING AGENTS	<i>Atorvastatin</i>
NARCOTICS	<i>Methadone</i>



PROTEASE INHIBITORS

3. Inhibitors of HIV integrase

e.g., **Raltegravir**

MOA:

- **Inhibiting HIV DNA integrase**, the enzyme that splices viral DNA into the host genome when forming provirus
- It prevents the formation of covalent bond between host and viral DNA

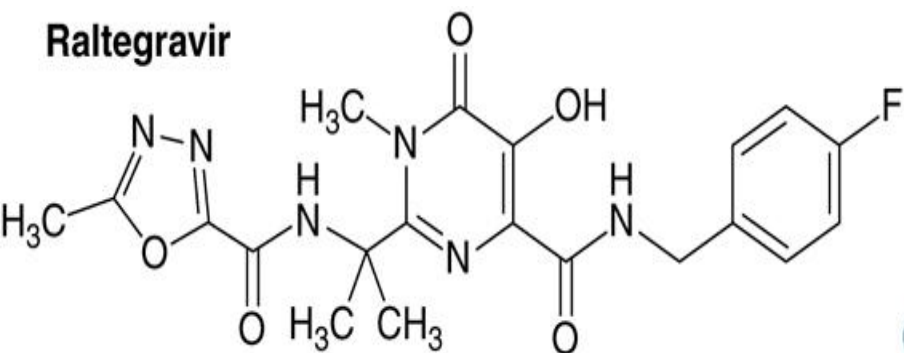
Used in:

- Resistance HIV as part of combination therapy

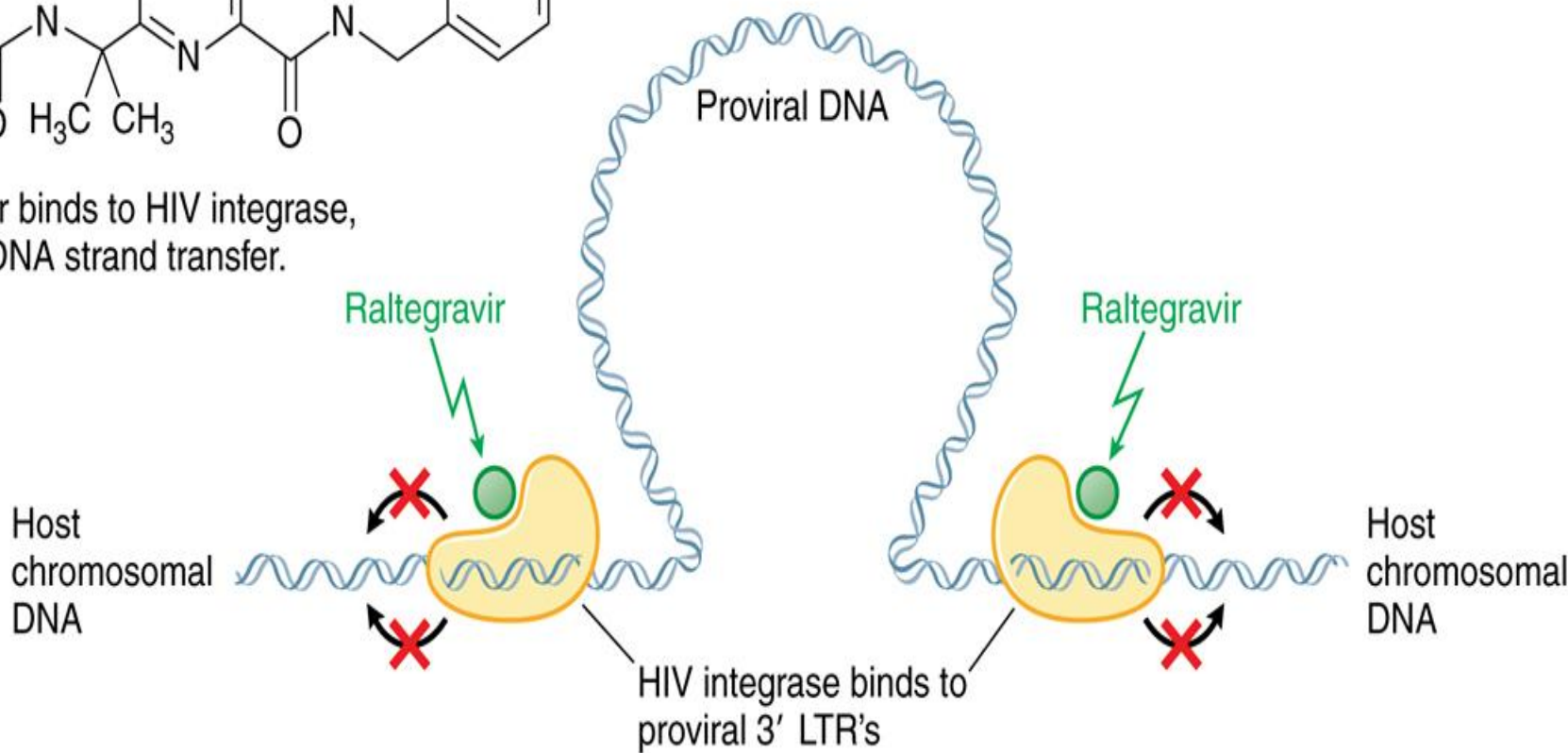
SE:

- Headache
- Fatigue
- Nausea

Raltegravir



Raltegravir binds to HIV integrase, prevents DNA strand transfer.



Mechanism of action of the HIV integrase inhibitor raltegravir

4. Inhibitors of viral fusion

E.g,

Enfurvirtide

MOA:

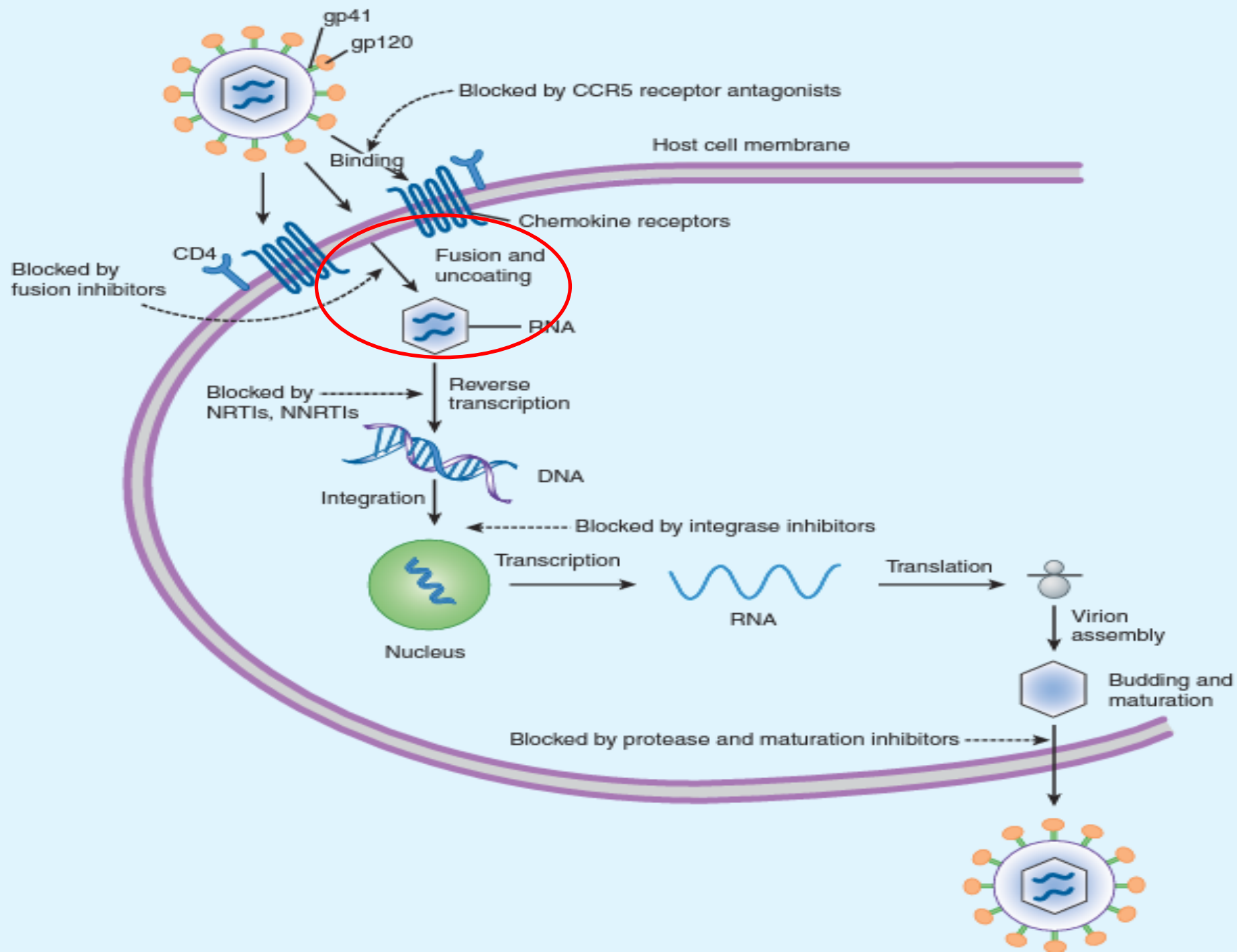
- Inhibits the fusion of HIV with host cells

Uses:

- Given SC in combination with other drugs to treat resistance HIV

SE:

- Flu like symptoms
- Hypersensitivity



5. Inhibitors of viral entry

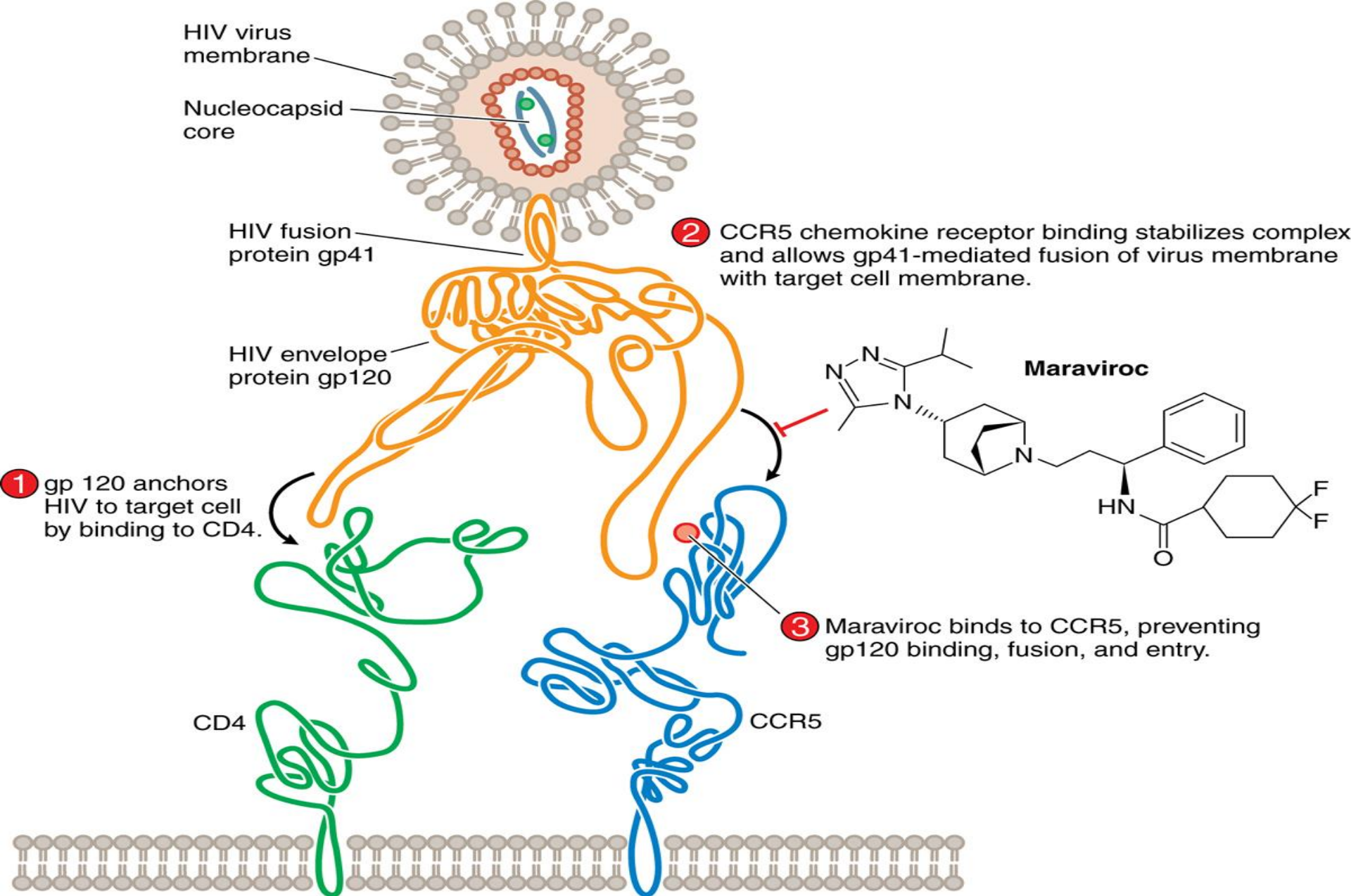
e.g., Maraviroc

MOA:

- It is **chemokine receptor antagonist**
- It binds to the host cell CCR5 receptor to block the binding of HIV

Note:

- **CCR5** is cell surface chemokine receptor that hijacked by some strains of HIV to gain entry to the cell



Mechanism of action of the HIV entry inhibitor maraviroc